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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/12/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/856,270	Chang et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 10, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-28 and 30-32* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-28 and 30-32* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 12-10-02 has been entered. Claims 1, 17, 19 and 30 have been amended. Claim 29 has been canceled. Claims 1-28 and 30-32 are pending and under consideration.

It should be noted that the examiner for the present application has been changed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-28 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering Tf-Adp53 vector expressing p53 to SCCHN xenograft on the lower back above the tail of nude mice via intravenous injection and reduction of tumor size while combined with radiation treatment, and delivering said Tf-Adp53 vector to immune competent B16 mouse of melanoma lung metastases model and reduction of lung metastases while combined with chemotherapy, does not reasonably provide enablement for a vector comprising a ligand other than transferrin non-covalently bound to a virus expressing a gene other than p53, a method for providing said vector to an animal for treating head and neck

cancer, bladder cancer, breast cancer, thyroid cancer, ovarian cancer, prostate cancer, melanoma or lymphoma with or without combination with radiation or chemotherapy, and a method for providing Tf-Adp53 to an animal for treating brain tumor with or without combination with radiation or chemotherapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-16 are directed to a vector for delivering a virus having a therapeutic nucleic acid encoding a protein, such as p53, to a target cell in a host animal, said vector comprises a cell-targeting ligand, such as a protein, a peptide, a hormone or an antibody etc., non-covalently bound directly to said virus. Claims 6-8 specify the virus is a retrovirus, an adenovirus, an AAV, HSV, CMV, a recombinant virus etc. Claim 11 specifies the ligand is EGF, FGF, a viral protein etc. Claim 12 specifies the ligand is transferrin. Claims 13-16 specify the ratio of cell-targeting ligand and virus. Claims 17 and 18 are directed to a method for preparing the vector set forth above by mixing the cell-targeting ligand with the virus in an aqueous medium, such as one or more of a buffering agent. Claims 19-28 and 30-32 are directed to a method for providing a nucleic acid therapeutic agent to an animal suffering from head and neck cancer, bladder cancer and breast cancer etc, as cited in the claims comprising administering to said animal the vector as set forth above for delivery of a virus comprising said therapeutic agent to a target cell within said animal. Claim 20 specifies the animal is a human. Claims 21-24 specify the agent is administered systemically, parenterally, intravenously and intratumorally. Claim 25 specifies the

vector encodes wild-type p53. Claim 26 specifies the ligand is transferrin. Claims 27, 28, 31 and 32 specify the therapeutic agent is administered in conjunction with chemotherapy or radiation treatment. Claims 30 specifies the virus encodes wild-type p53 and the ligand is transferrin and said therapeutic agent is administered systemically.

The specification discloses delivering Tf-Adp53 vector expressing p53 to SCCHN xenograft on the lower back above the tail of nude mice via intravenous injection and reduction of tumor size while combined with radiation treatment, and delivering said Tf-Adp53 vector to immune competent B16 mouse of melanoma lung metastases model and reduction of lung metastases while combined with chemotherapy. The claims encompass a vector comprising any cell-targeting ligand non-covalently bound to a virus expressing any gene, and a method for providing said vector to an animal for treating head and neck cancer, bladder cancer, breast cancer, thyroid cancer, ovarian cancer, prostate cancer, melanoma or lymphoma with or without combination with radiation or chemotherapy *in vivo*.

The specification states that "The present invention relates to improvements to gene transfer and gene therapy technology. More specifically, the invention provides composition and methods for targeted *in vitro* and *in vivo* viral delivery of nucleic acids into human and other animals to a specific organ, tissue, or tumor" (page 1, lines 6-9). The only use for the claimed vectors as disclosed in the specification is to improve gene transfer and gene therapy technology. Thus, the claims read on gene transfer *in vivo*.

The specification fails to provide adequate guidance and evidence for how to treat a brain tumor in an animal, including a human, with the claimed vector having a cell-targeting ligand non-covalently bound to a virus encoding any therapeutic protein or agent via various administration routes. It was well known in the art that brain is separated from general circulation by the blood brain barrier. Castro et al., 2001 (Histl. Histopathol., Vol. 16, p. 1225-1238) points out that the brain offers a particular challenge for gene delivery to its constituent cells because it is "made up of mostly non-dividing cells, the skull limits direct injection of vectors into the brain, the blood brain barrier inhibits the easy entry of vectors injected into the bloodstream, and post mitotic target cells restrict what type of vector can be used to deliver genes to the brain" (e.g. abstract). "The main challenges holding back the widespread clinical implementation of neurological gene therapy are technical limitations of current transgene delivery system, i.e. the gene transfer vectors...short term expression of the potentially therapeutic transgenes, coupled to the instability of vectors in the presence of the inflammatory and immune responses directed against the vectors and/or transgenes, reduce the efficiency of delivered therapeutic transgenes...Factors affecting vector stability in target cells/tissues, remain to be identified" (e.g. page 1226, right column). The specification fails to provide adequate guidance and evidence that delivery of the claimed vector comprising any cell-targeting ligand and a virus expressing any therapeutic agent via various administration routes could provide therapeutic effect for various brain tumors within an animal, including a human. In view of the

reasons set forth above, one skilled in the art at the time of the invention would not know how to use the claimed vector to treat various brain tumors in an animal.

Claim 19 specifies the animal is human. The specification fails to provide adequate guidance and evidence for how to deliver the claimed vector to a human for treating various cancers, such as breast cancers, prostate cancers, brain tumors etc., and said delivery would result in sufficient expression of the therapeutic product so as to provide therapeutic effect said human. There is difference between animal models and human beings. The experimental data of animal models can not always be extrapolated to human studies. Orkin et al., 1995 (Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene therapy) states that "Unfortunately, however, mouse model often do not faithfully mimic the relevant human conditions (page 11, see full paragraph), and that "It is not always possible to extrapolate results from experiments in animals to human studies. This difficulty is particularly evident with respect to the efficiency of gene delivery and the host response to viral vectors...Animal models are not satisfactory for studying many important human disorders..." (Page 14, fourth and fifth paragraphs). Further, Gura (Science, Vol. 278, p. 1041-1042, 1997) reports "The fundamental problem in drug discovery for cancer is that the (animal) model systems are not predictive at all" and "The animals apparently do not handle the drugs exactly the way the human body does. And attempts to use human cells in culture don't seem to be faring any better, partly because cell culture provides no information about whether a drug will make it to the tumor site" (e.g. p. 1041, first column). There is no evidence of record that delivery of the claimed vector to a

human patient for treating any cancer via any administration route would provide therapeutic effects in said patient. Thus, one skilled in the art at the time of the invention would not know how to use the claimed vector to treat any cancer in a human patient.

The specification also fails to provide adequate guidance and evidence for how to deliver the claimed vector comprising numerous different cell-targeting ligands, such as proteins, peptides, hormones, antibodies and antibody fragments etc., and a virus encoding numerous different therapeutic agents to an animal having various cancers such that the delivery of said vector to said animal via various administration routes with or without combination with chemotherapy or radiation treatment could provide therapeutic effect in said animal. The specification fails to provide guidance as which type of tumors contain over-expressed transferrin receptor or other claimed ligand receptors. A ligand mediated cell targeting can only succeed when the ligand is used for delivering a therapeutic gene to a tumor type over-expressing the ligand receptor. IN addition, the specification fails to provide adequate guidance for the correlation of the nucleic acid encoding a specific therapeutic protein or peptide with a particular cancer type in an animal such that delivery of said nucleic acid can provide therapeutic effect for the treatment of said particular cancer *in vivo*.

While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art as discussed above un Castro et al., and Orkin et al. Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will

concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene transfer (e.g. bridging pages 81-82). In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to deliver the claimed vector comprising numerous different cell-targeting ligands, such as proteins, peptides, hormones, antibodies and antibody fragments etc., and a virus encoding numerous different therapeutic agents to an animal having various cancers such that the delivery of said vector to said animal via various administration routes with or without combination with chemotherapy or radiation treatment could provide therapeutic effect for a particular cancer in said animal.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-4, 6, 8-11, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Douglas et al., 1997 (International Journal of Oncology, Vol. 11, p. 341-348).

Claims 1-4, 6 and 8-11 are directed to a vector for delivering a virus having a therapeutic nucleic acid encoding a protein or peptide to a target cell in a host animal, said vector comprises a cell-targeting ligand, such as a protein, a peptide, a hormone or an antibody etc., non-covalently bound directly to said virus. Claims 6 and 8 specify the virus is a retrovirus, an adenovirus, or a

recombinant virus. Claim 11 specifies the ligand is EGF, FGF, a viral protein etc. Claims 17 and 18 are directed to a method for preparing the vector set forth above by mixing the cell-targeting ligand with the virus in an aqueous medium, such as one or more of a buffering agent.

Douglas teaches generation of an adenovirus complex by conjugating folate to the neutralizing Fab fragment of an anti-knob monoclonal antibody and the Fab-folate conjugate was complexed with an adenovirus AdCMVLuc, and shows said adenovirus complex redirect adenoviral infection of a human nasopharyngeal carcinoma cell specifically via the folate receptor. Douglas also teaches generation of an adenovirus complex by conjugating FGF2 to the neutralizing Fab fragment of an anti-knob monoclonal antibody and the Fab-FGF2 conjugate was complexed with an adenovirus AdCMVLuc (e.g. p. 343, 344). Douglas suggests the adenovirus complex set forth above can be used for delivering HSV-TK gene in cancer gene therapy (e.g. p. 341, right column). Folate and FGF2 are cell-targeting ligands and they are non-covalently bound to adenovirus. Thus, claims 1-4, 6, 8-11, 17 and 18 are anticipated by Douglas.

5. Claims 1-4, 6, 8-10, 12, 17 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Woo et al., 1999 (US Patent 5,994,109).

Claims 1-4, 6, 8-10 and 12 are directed to a vector for delivering a virus having a therapeutic nucleic acid encoding a protein or peptide to a target cell in a host animal, said vector comprises a cell-targeting ligand, such as a protein, a peptide, a hormone or an antibody etc., non-covalently bound directly to said virus. Claims 6 and 8 specify the virus is a retrovirus, an

adenovirus, or a recombinant virus. Claim 12 specifies the cell-targeting ligand is transferrin. Claims 17 and 18 are directed to a method for preparing the vector set forth above by mixing the cell-targeting ligand with the virus in an aqueous medium, such as one or more of a buffering agent.

Woo teaches "Nucleic acid transporter systems for delivery of nucleic acid to a cell. The nucleic acid transporter includes a binding complex. The binding complex contains a binding molecule which non-covalently binds to the nucleic acid and covalently links to a surface ligand, nuclear ligand and/or a lysis agent" (abstract). The nucleic acid includes naked DNA, a nucleic acid cassette and viruses etc. (Column 5). The binding molecule can non-covalently bind to nucleic acid, such as viruses, and the binding molecule also can covalently link to a ligand. The binding molecule includes polylysine, polyamines and **cationic peptides** etc. (Column 6). The viruses used for gene therapy include retroviruses and adenoviruses (column 1). Woo also teaches using transferrin and the transferrin receptor for delivery of DNA to cells in vitro (column 3). The cationic peptide is considered a ligand, which can non-covalently bind to viruses, and it can bind to other ligand for cell-specific delivery of nucleic acid. The buffer solution for preparing the binding complex is an aqueous solution. Thus, claims 1-4, 6, 8-10, 12, 17 and 18 are anticipated by Woo.

6. Claims 1-4, 6-10 and 19-24 remain rejected under 35 U.S.C. 102(e) as being anticipated by Wickhan et al., 1999 (US Patent 5,962,311) and is repeated for the reasons set forth in the

preceding Official action mailed 8-14-02 (Paper No. 8). Applicant's arguments filed 12-10-02 have been fully considered but they are not persuasive.

Applicants argue that the patent does not teach or suggest noncovalantly and directly binding a transferrin molecule to a virus containing a therapeutic nucleic acid for in vitro or in vivo delivery of nucleic acid to target cells containing a transferrin receptor (amendment, p. 11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-14-02 (Paper No. 8) and that claims 1-4, 6-10 and 19-24 do not specify the cell-targeting ligand must be transferrin, in fact, the claims encompass any protein, peptide, hormone or any antibody as a cell-targeting ligand. Further, Wickham demonstrate delivery of alkaline phosphatase gene to 293 cells by using AdSE.F5F9Kshort (example 7). Thus, claims 1-4, 6-10 and 19-24 remain rejected under 35 U.S.C. 102(e).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 5, 25, 27 and 28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wickhan et al., 1999 (US Patent 5,962,311) in view of Zhang et al., 2002 (US Patent 6,410,010) and is repeated for the reasons set forth in the preceding Official action mailed 8-14-02 (Paper No. 8). Applicant's arguments filed 12-10-02 have been fully considered but they are not persuasive.

Applicants cite same arguments as set forth above under 35 U.S.C. 102(e) rejection. This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-14-02 (Paper No. 8) and the reason set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.